REVIEW

Purkinje-related Arrhythmias Part II: Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

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There has been growing evidence that the Purkinje network plays a pivotal role in both the initiation and perpetuation of ventricular fibrillation (VF). A triggering ventricular premature beat (VPB) with a short-coupling interval could arise from either the right or left Purkinje system in patients with polymorphic ventricular tachycardia (VT) or VF, and that can be suppressed by the catheter ablation of the trigger. A focal breakdown in the "gating mechanism" at the Purkinje system resulting in a short-circuiting of the transmission across the gate at the distal Purkinje network might predispose to reentrant circuits of polymorphic VT/VF. Many investigators also reported the successful ablation of Purkinje-related VF with an acute or remote myocardial infarction. The same approach with good short-term results has been reported in a small number of patients with other heart diseases (i.e., amyloidosis, chronic myocarditis, nonischemic cardiomyopathy). Catheter ablation of the triggering VPBs from the Purkinje system can be used as an electrical bailout therapy in patients with VF storm. (PACE 2011; 34:1034–1049)

catecholaminergic polymorphic ventricular tachycardia*, *catheter ablation*, *His-Purkinje system*, *myocardial infarction*, *myocarditis*, *polymorphic ventricular tachycardia*, *Purkinje potential*, *reentry*, *short-coupled variant of torsade de pointes*, *triggered activity*, *ventricular fibrillation

Introduction

In the last two decades, there has been rapid progress in the treatment of ventricular arrhythmias and the Purkinje system has been found to be responsible for the mechanism of some ventricular tachyarrhythmias. These ventricular tachyarrhythmias can be called Purkinje-related arrhythmias, and monomorphic ventricular tachycardia (VT) and polymorphic VT, including ventricular fibrillation (VF), are such. This manuscript, the second part of Purkinje-related arrhythmias, focuses on the assessment and treatment of polymorphic VT and VF.

History and Classification

Although previous studies have shown that VF is perpetuated by reentry or spiral waves, recent data suggest the role of specific sources in triggering this arrhythmia.[1–3] In 2002, Haïssaguerre et al. reported that idiopathic VF could be suppressed by catheter ablation of triggers originating from the Purkinje system.[4,5] This idiopathic VF or polymorphic VT was associated with a short-coupling interval between ventricular premature beats (VPBs) and conducted complexes.[6] The Purkinje system may also play a role in postinfarction VF. In 2002, Bänsch et al. reported that in patients with repetitive VF following an acute myocardial infarction (MI), Purkinje signals preceded every VPB, ablation of the sites of the Purkinje signals eliminated all VPBs, and no VF recurred during the follow-up.[7] Recent mapping studies have shown that Purkinje fibers can initiate VF in some patients with other structural heart diseases: Brugada syndrome,[8] Long-QT syndrome,[8] amyloidosis,[9] chronic myocarditis,[10] ischemic cardiomyopathy,[10–15] nonischemic cardiomyopathy,[16] and catecholaminergic polymorphic VT (CPVT) (Table I).[17]

Idiopathic Purkinje-Related VF (Short-Coupled Variant of Torsade de Pointes)

Catheter Ablation

Leenhardt et al. were the first to describe a syndrome of polymorphic VT associated with a short-coupling interval (245 ± 28 ms) between VPBs and conducted complexes in patients without ischemic or structural heart disease.[6] This arrhythmia could not be provoked by isoproterenol, but the coupling interval lengthened in all patients after verapamil. Verapamil was the only drug apparently active on the arrhythmias; however, it did not prevent sudden death. Haïssaguerre et al. then showed that this triggering VPB with a short-coupling interval could arise from either the right or left Purkinje system in 23 patients with

Disclosures: None.

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Received February 20, 2011; revised March 29, 2011; accepted April 21, 2011.

doi: 10.1111/j.1540-8159.2011.03145.x

Table I.

Purkinje-Related Polymorphic VT/VF

I.	Idiopathic VF (short-coupled variant of torsade de pointes)
	i. Left distal Purkinje origin[4,5,18,21]
	ii. Right distal Purkinje origin[4,5,19,20]
II.	Ischemic heart disease
	i. Acute MI[7,10,11,36]
	ii. Remote MI or ischemic cardiomyopathy[11–15]
III.	Chronic myocarditis[10]
IV.	Amyloidosis[9]
V.	Nonischemic cardiomyopathy[16]
VI.	Aortic valve disease[10]
VII.	Brugada syndrome[8]
VIII.	Long-QT syndrome[8]

MI = myocardial infarction; VT = ventricular tachycardia; VF = ventricular fibrillation.

idiopathic polymorphic VT or VF.[5] The interval from the Purkinje potential to the myocardial activation during sinus rhythm was 11 ± 5 ms, suggesting that the recordings were obtained from the distal Purkinje fibers. The Purkinje potential was recorded 38 ± 28 ms before the VPB. Ablation of the trigger resulted in a high cure rate of 89%. However, little is still known about the initiating mechanism of VF or the mechanism of the ablation effect.

Figure 1 shows the electrocardiograms from our patient with a short-coupled variant of torsade de pointes.[18] Isolated VPBs were rarely observed and had a right bundle branch block (RBBB) configuration and right-axis deviation (Fig. 1A). Holter monitoring revealed multiple episodes of polymorphic VT (mean cycle length 222 ms; Fig. 1B). Polymorphic VT was consistently initiated by an early-coupled VPB (coupling interval of 260 ms) and the morphologies of the first two QRS complexes of the polymorphic VT were always the same on each occasion. In the electrophysiologic laboratory, nonsustained polymorphic VT with the same QRS morphology as the clinical polymorphic VT was repeatedly inducible by atrial pacing. The first VPB (VPB1) had an RBBB configuration with right-axis deviation. The second VPB (VPB2) had an RBBB pattern with a northwest axis.

During the polymorphic VT, diastolic and presystolic Purkinje potentials were recorded from the left ventricular septum (Fig. 2). During sinus rhythm, the recording at the same site demonstrated fused Purkinje potentials before the onset of the QRS. Bipolar pace mapping was performed from an electrode catheter at the left ventricular septum (Fig. 3). Stimulation from electrodes[5,6] did not directly capture the ventricular muscle but captured the Purkinje tissue. The paced QRS configuration was not similar to that of VPB1 (Fig. 3A) and there was no potential between the pacing stimulus and

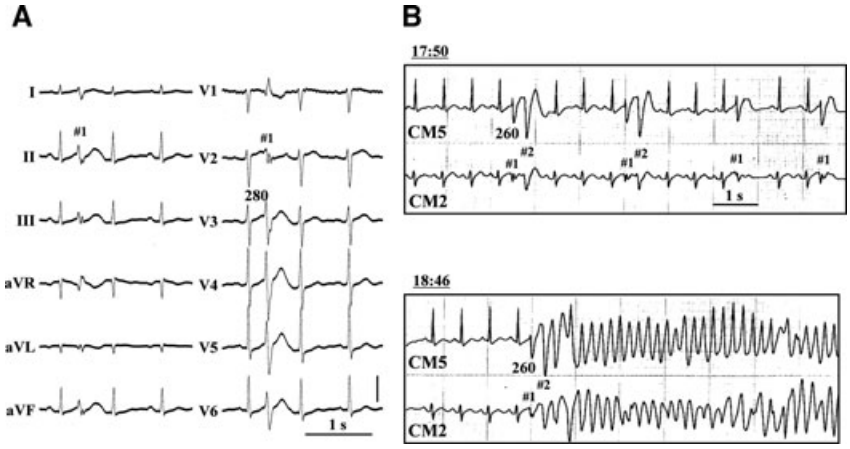

Figure 1. *Twelve-lead ECG and Holter monitoring in a patient with a short-coupled variant of torsade de pointes. (A) Electrocardiogram with normal sinus rhythm. Isolated VPBs were rarely recorded. The VPB had a right bundle branch block configuration with a right-axis deviation. The coupling interval to the preceding normally conducted QRS was 280 ms. (B) Episodes recorded during Holter monitoring. Multiple episodes of polymorphic ventricular tachycardia (VT) (mean cycle length 222 ms) with syncope were recorded. Polymorphic VT was consistently initiated by an early-coupled VPB (coupling interval 260 ms). The morphologies of the first two QRS complexes (VPB1 and VPB2) of the polymorphic VT were always the same on each occasion. Two channel recordings (CM5 and CM2) were recorded. From Nogami et al.[18] with permission.*

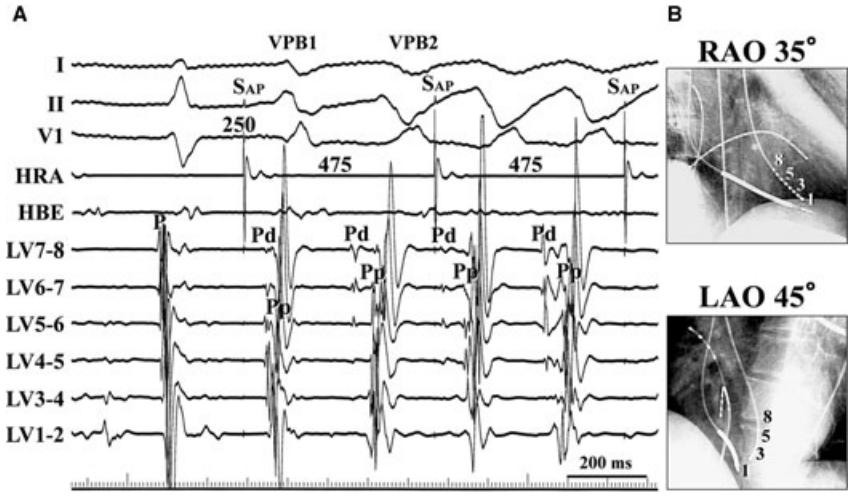

Figure 2. *Catheter mapping during polymorphic ventricular tachycardia. (A) During polymorphic VT, a diastolic Purkinje potential (Pd) and presystolic Purkinje potential (Pp) were recorded from the left ventricular septum. During sinus rhythm, fused Purkinje potentials (P) were recorded before the QRS onset. (B) Representation of an octapolar electrode catheter placed on the left ventricular septum. HBE = His-bundle electrogram; HRA = high right atrium; LAO = left anterior oblique view; LV = left ventricle; P = Purkinje potential during sinus rhythm; Pd = diastolic Purkinje potential; Pp = presystolic Purkinje potential; RAO = right anterior oblique view; S_{AP} = atrial pacing stimulus; VPB = ventricular premature beat. From Nogami et al.[18] with permission.*

the ventricular activation (Fig. 3B). Pacing at the same site with a higher output produced a QRS configuration similar to that of VPB1 (Fig. 3C). In this pace mapping, presystolic Purkinje potentials were recorded between the pacing stimulus and ventricular activation. These phenomena indicate that the orthodromic activation of the presystolic Purkinje potential reproduced a QRS morphology identical to VPB1. Radiofrequency (RF) energy was delivered to the site of electrodes.[3,4] Electrograms recorded after the ablation revealed the abolition of the local Purkinje potential at the middle portion and a slight delay in the occurrence of the local ventricular electrogram during sinus rhythm (Fig. 3D). The activation of the distal Purkinje system and septal muscle was delayed and reversed (retrograde), suggesting a collateral activation from the distal Purkinje network. After the ablation the polymorphic VT became noninducible, and only an isolated VPB was induced. The morphology of this VPB differed from that of the previous trigger VPBs but was similar to that during the pace mapping at the ablation site with a lower output (Fig. 3B). Holter monitoring after the ablation revealed no VPBs. No episodes of syncope or VF occurred during a 10-year follow-up.

Trigger VPBs in idiopathic VF can also arise from the right Purkinje system. Haïssaguerre et al. reported that VPBs were elicited from the left ventricular septum in 10, from the right ventricle in nine, and from both in four of their 23 patients.[5] While the trigger VPBs from the left Purkinje fiber could be ablated at left ventricular septum, the VPBs from the right distal Purkinje fiber were elicited at the right ventricular free wall.

Figure 4 shows the intracardiac electrograms during polymorphic VT in a patient who experienced a VF storm. The trigger VPB (VPB1) had a left bundle branch block (LBBB) configuration with a superior axis. The second VPB (VPB2) also had an LBBB with a superior axis; however, the QRS morphology slightly differed from VPB1. During polymorphic VT, a presystolic Purkinje potential was recorded from the right ventricular apical free wall. The presystolic Purkinje potential preceded the trigger VPB1 by 20 ms. During sinus rhythm, no Purkinje potentials were recorded before the normally conducted QRS. Saliba et al.[19] and Kohsaka et al.[20] also reported a successful ablation of trigger VPBs from the right distal Purkinje fiber. Their successful ablation sites were the infero-lateral border of the right ventricle and right ventricular anterior wall, respectively. In both cases, no Purkinje potentials were recorded before the normally conducted QRS during sinus rhythm. The distal right Purkinje potential might be buried in the local muscular activation during sinus rhythm. While VPBs originating from the left Purkinje system produce variable 12-lead

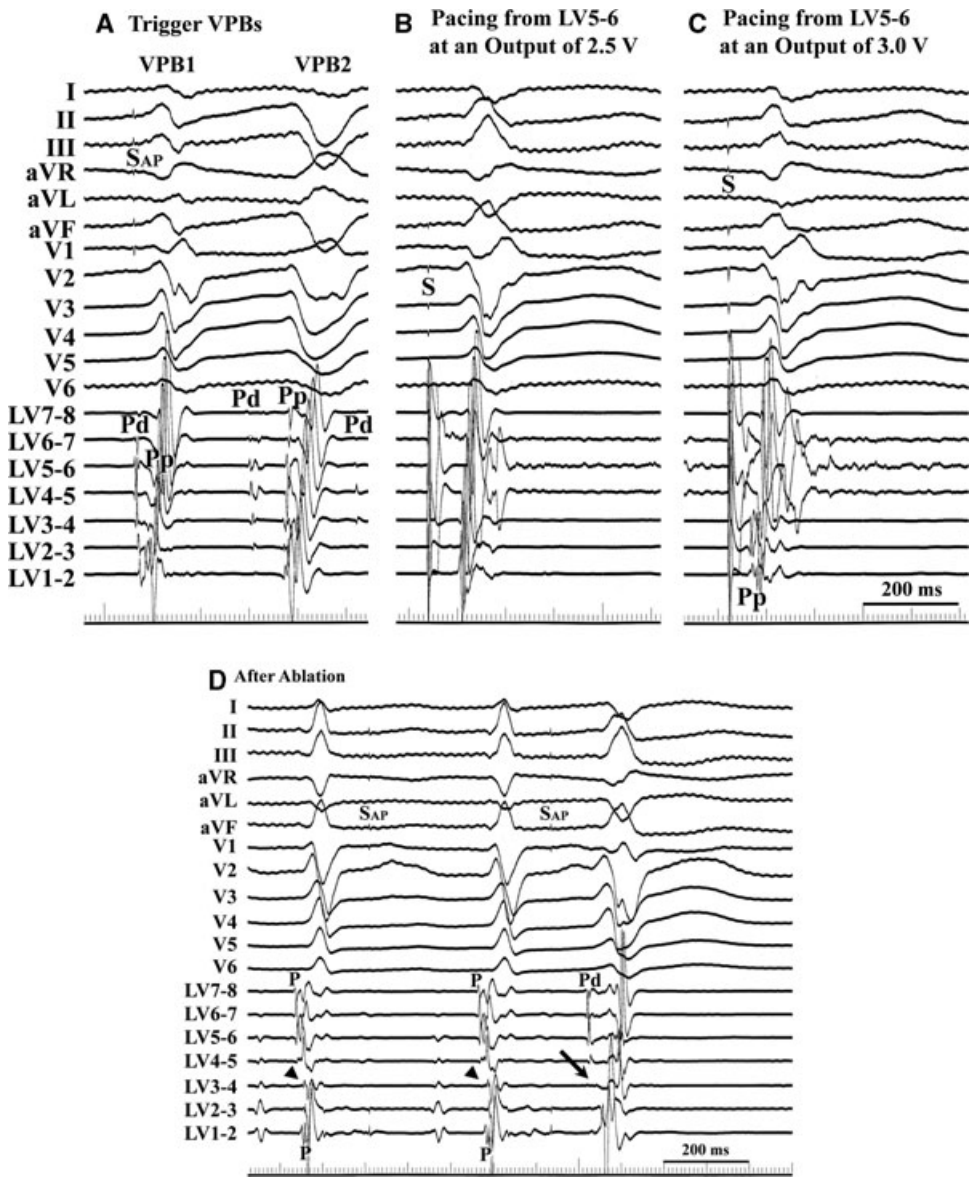

Figure 3. *Pace mapping and electrograms after ablation. (A) The first two VPBs (VPB1 and VPB2) triggering the polymorphic VT. (B) Pacing from electrodes LV5–6 did not directly capture the ventricular muscle but captured the Purkinje tissue. The paced QRS configuration was not similar to that of VPB1. (C) Pacing from electrodes LV5–6 with a higher output reproduced a similar QRS configuration to that of VPB1. Presystolic Purkinje potentials were recorded between the pacing stimulus and ventricular activation. (D) Induction of the tachycardia after ablation. Electrograms recorded after ablation showed the abolition of the local Purkinje potential (P) at the middle portion and a slight delay in the occurrence of the local ventricular electrogram during sinus rhythm (arrow head). The polymorphic VT became noninducible and only an isolated VPB was inducible. The morphology of this VPB differed from that of the previous trigger VPB and intra-Purkinje block was also observed before this VPB (arrow). LV = left ventricle; P = Purkinje potential during sinus rhythm; Pd = diastolic Purkinje potential; Pp = presystolic Purkinje potential; S = ventricular pacing stimulus for pace mapping; S_{AP} = atrial pacing stimulus. From Nogami et al.[18] with permission.*

electrocardiogram (ECG) patterns, VPBs originating from the right Purkinje system typically have an LBBB pattern with a left superior axis.[21] This may be due to a more complex and extended Purkinje arborization on the left. The Purkinje network consists of a single branch on the right that penetrates a limited portion of the right ventricle, and at least two larger branches on the left that ramify more intricately to supply a greater area of the left ventricle.[22–24]

Practical Approach to Map and Ablate the Purkinje System

Mapping and ablation of the left Purkinje system may be performed by the transaortic (retrograde) or the transseptal approach. Transseptal approach can be used in a patient with significant kinking of the aorta. Usually, transaortic approach is superior to map the left ventricular septum and stabilize the ablation catheter. When a transseptal approach is needed, a long steerable sheath is useful. In patients with frequent VPBs resembling the VPB morphology that initiated polymorphic VT or VF, three-dimensional (3D) activation mapping of the VPBs may be performed. If no spontaneous VPBs were detected, VPBs can be induced by the use of pacing maneuvers (ventricular burst or extrastimuli) and/or isoproterenol or adenosine or phenylephrine infusion. Burst atrial pacing after atropine is also useful to induce trigger VPBs. Careful attention has to be made to identify any low-amplitude, high-frequency, Purkinje-like potential preceding the VPBs. During sinus rhythm, the location of the Purkinje network is indicated by initial sharp potentials (<10-ms duration) preceding the QRS. In addition, pace mapping may be done as a supplemental tool to localize ablation targets. For this purpose, 12-lead ECG documentation of the all-trigger VPBs should be done prior to the ablation session with the same ECG lead positions as in the electrophysiology laboratory. RF ablation was performed with a cooled-tip ablation catheter. However, very high power is usually not needed, because the Purkinje network is very easily ablated. Mapping and ablation of the right Purkinje system can be performed using the standard method and a long sheath. While the trigger VPBs from the left Purkinje fiber are detected at left ventricular septum, the VPBs from the right distal Purkinje fiber usually originate at the right ventricular free wall. The distal right Purkinje potential may be buried in the local muscular activation during sinus rhythm.

Mechanism

In our patients, a rapid polymorphic VT was initiated by VPBs with very short-coupling intervals. Further, a polymorphic VT with the same QRS morphology as the spontaneous polymorphic VT was inducible by burst atrial pacing (i.e., Purkinje stimulation) and was suppressed by verapamil. These observations suggest that the VF initiation might be caused by triggered activity from Purkinje tissue. However, suppression of VF was achieved with catheter ablation of the Purkinje network, not the earliest Purkinje activation in this patient. Therefore, we hypothesized that the reentry in the Purkinje system is essential for the initiation of VF. In the report by Haïssaguerre et al., the electrocardiograms recorded after the ablation showed the abolition of the local Purkinje potential and a slight delay in the occurrence of the local ventricular electrogram.[5] However, they did not determine how much of the complex Purkinje network was involved in each patient and the issue of multiple foci versus differing activation routes from limited foci remains unsolved. In our patient with the trigger VPBs from the left Purkinje network, catheter mapping revealed that the constantly changing polymorphic QRS morphology resulted from the changing propagation in the Purkinje arborization and the polymorphic VT became noninducible after the catheter ablation of the Purkinje network. In the presented case, we did not ablate the earliest site of the Purkinje activation, and an isolated VPB with diastolic Purkinje activation was still inducible after the catheter ablation. Knecht et al. also reported that a recurrence of clinical VPBs after ablation was observed in two of 38 patients with idiopathic VF that no longer resulted in malignant ventricular arrhythmias.[21] They speculated that modulation of the Purkinje system and its surrounding tissue may be sufficient in some cases for avoiding initiating VF.

As possible mechanisms for the short-coupled variant of torsade de pointes, Scheinman[25] speculated that Ca^{2+} overload in the Purkinje tissue results in delayed afterdepolarizations, which lead to reentry in the Purkinje network due to a defective gate function as proposed by Myerburg et al.[23,26,27] The experimental studies by Myerburg et al. showed that the action potential duration and refractoriness of the peripheral Purkinje fibers gradually prolonged, with the maximal action potential duration occurring 2–3 mm proximal to the Purkinje-muscle junction.[23,26] In addition, they found that these areas of maximal refractoriness acted as gates for impulses propagated from above (Fig. 5).[26] They found that the "gates" were similar to multiple Purkinje strands, providing a "uniform functional limit for the propagation of premature impulses across the distal end of the conduction system." Moreover, approximately timed premature Purkinje or ventricular impulses could be confined either proximal or distal to the gate. A focal breakdown in the gating

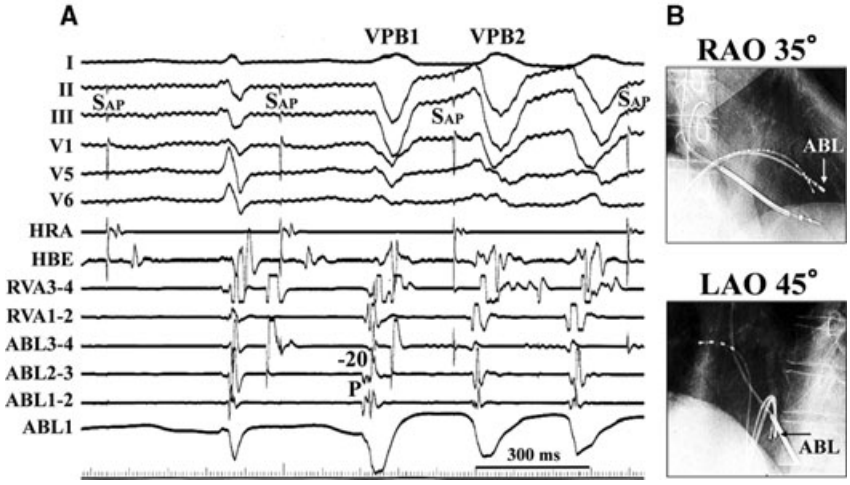

Figure 4. *Catheter mapping during polymorphic ventricular tachycardia from right Purkinje system. (A) During polymorphic VT, a presystolic Purkinje potential (P) was recorded from the right ventricular apical free wall. The presystolic Purkinje potential preceded the trigger VPB1 by 20 ms. During sinus rhythm, no Purkinje potential was recorded before the normally conducted QRS. Note that the activation sequences during VPB1 and VPB2 differed. (B) Representation of an ablation catheter (ABL) placed on the right ventricular apical free wall. ABL = ablation catheter; HBE = His-bundle electrogram; HRA = high right atrium; LAO = left anterior oblique view; P = Purkinje potential; RAO = right anterior oblique view; RVA = right ventricular apex; S_{AP} = atrial pacing stimulus.*

mechanism could result in a short-circuiting of the transmission across the gate, predisposing to reentrant circuits (Fig. 6).[23] They also evaluated the influence of incised lesions in the left conducting system on the patterns of activation (Fig. 7).[27] While there was a minimal delay in the activation in the conducting system and almost no delay in the sequence of the muscle activation when an incised lesion was made close to the bifurcation on the main left bundle branch (Fig. 7B), the activation of the conducting system was delayed and reversed (retrograde), and the activation of the posterobasal septal muscle was markedly delayed when a vertical incision was added to the lower third of the septum so as to cut through the interconnecting subendocardial Purkinje fibers (Fig. 7C). These electrograms after the Purkinje network incision in Myerburg's experiment are quite similar to the electrograms after the successful ablation of the Purkinje network in our patient (Fig. 3D).

Other investigators have explored the role of the Purkinje fibers in the initiation and maintenance of VF or polymorphic VT using experimental models. In 1998, Berenfeld and Jalife used a computerized 3D model to test the hypothesis that reentry involving the Purkinje muscle junction may be a mechanism of focal subendocardial activation during polymorphic VT.[28] In addition to the capacity for triggered activity, the differences between the Purkinje fibers and myocardium in the upstroke velocity, intracellular coupling, and action potential duration may provide the conditions for initiating or sustaining VF. And finally, the reentry was terminated if the Purkinje system was disconnected from the muscle before it reached a relative steady state of VF. Their model supported the possibility that Purkinje fibers are involved in the evolution and maintenance of reentry during polymorphic VT. In experiments performed in isolated canine hearts, multielectrode mapping of the endocardial left ventricle has shown a focal initiating mechanism for VF in 34%, of which 42% arose from Purkinje fibers.[29] Dosdall et al. demonstrated that the Purkinje system is active during early postshock activation cycles in pigs[30] and the ablation of the Purkinje system by Lugol's solution hastened spontaneous VF termination.[31] Pak et al. demonstrated the differences in the effect of Purkinje ablation and the distribution of the Purkinje network in dogs and swine.[32,33] While the VF inducibility was decreased by catheter ablation targeting the left ventricular posteroseptal endocardium in dogs, the same ablation procedure did not reduce the VF inducibility in swine. In contrast to the canine Purkinje network, which is mostly localized to the subendocardium, the swine Purkinje network extends to the subepicardial layer with a higher density (Fig. 8).[34] Ideker

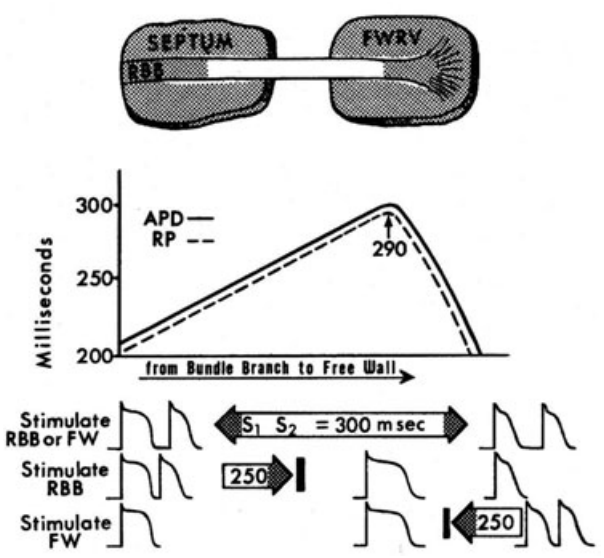

Figure 5. *The gating mechanism. The preparation (top) consisted of a single free-running false tendon from the right bundle branch (RBB) to the free wall of the right ventricle (FWRV). The graph demonstrates that the changes in the action potential duration (APD) along the length of the preparation are paralleled by the changes in the local refractory period (RP). There is a progressive increase in the APD and RP to a maximum of 290 ms and a sharp fall as the conduction fibers approach the free wall. The functional refractory period of the preparation is the minimum coupling interval (S1–S2), which can result in excitation of the FW by the premature impulse applied to the RBB. The duration of the functional refractry period is determined by the duration of the local refractory period at the area of the maximum action potential duration, or gate. From Myerburg et al.[26] with permission.*

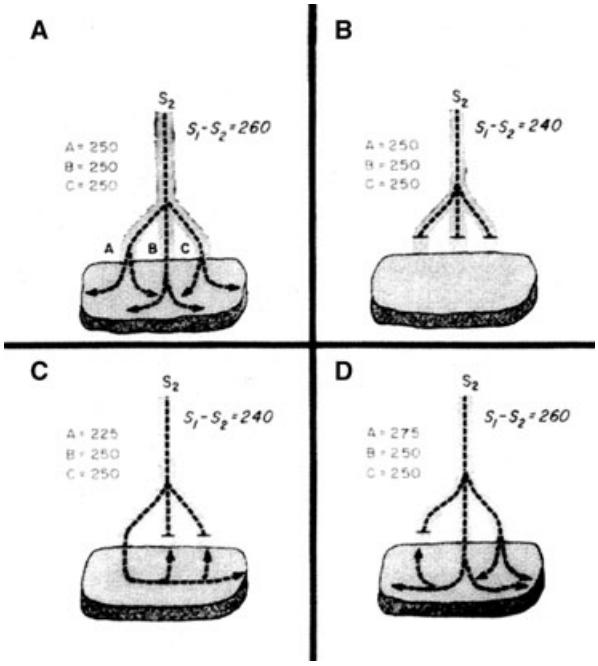

Figure 6. *Hypothetical patterns of normal and abnormal function of the gating mechanism. The diagram represents a false tendon with three branches serving the ventricular myocardium. Panels A and B demonstrate the normal situation in which the gates of all three branches have the same refractory period of 250 ms. (A) The premature impulse occurs 260 ms after the driving impulse (S1), and therefore finds all gates able to conduct the impulse. (B) The premature impulse occurs early enough to find all gates refractory, and the descending impulse is not conducted. (C) The gate of branch A is abnormally short and at the same S1–S2 interval that caused block in all branches in panel B, the impulse is able to bypass the normal gates of the system and depolarize the myocardium. (D) The gate of branch A has an abnormally long refractry period and is not crossed by the premature impulse with the same S1–S2 interval as that in panel A. Under appropriate conditions of the timing and conduction velocities, this could set the stage for a reentrant arrhythmia. From Myerburg et al.[23] with permission.*

and colleagues examined transmural activation mapping during long-duration VF in swine and canines, and documented that the difference in the Purkinje distribution had a significant impact on the transmural VF activation pattern.[35] Figure 9 shows the electrograms at 2, 6, and 10 minutes of VF. In pigs, the activation rate slows from 2 to 10 minutes of VF, but continues at a similar rate at all six electrodes transmurally as the VF continues. In dogs, the activation rate slows near the epicardium more than near the endocardium. Conduction block in the dog first occurs toward the epicardium and progresses with time toward the endocardium. This transmural mapping during VF explains why the Purkinje network ablation from the endocardium in swine did not reduce the VF inducibility in the experiment by Pak et al.[32,33]

Long-Term Results after Ablation

A multicenter study reported the long-term follow-up of 38 patients who underwent catheter ablation of VPB triggers for idiopathic VF.[21] During a median follow-up of 63 months, seven patients (18%) had recurrent VF. Five of the seven patients underwent a repeat procedure with a successful ablation of the VPB triggers. Different VPBs were demonstrated in four of five patients, and an identical VPB was demonstrated in the remaining patient. Despite the impressive clinical

success rate of this therapeutic paradigm, an important practical limitation is the unknown frequency at which these patients can be identified. These patients appear to represent a highly selected cohort, thereby rendering VF ablation a rarity.

Purkinje-Related VF in Ischemic Heart Disease

Catheter Ablation

In 2002, Bänsch et al. reported successful catheter ablation of electrical storm (combinations of VF and monomorphic VT) in four patients following an acute MI.[7] The time between the onset of the MI and the occurrence of VF was 1–7 days. Purkinje signals preceded every trigger VPB, and ablation of the sites of the Purkinje signals eliminated all VPBs and no VT or VF recurred during a follow-up of 16 ± 5 months. The coupling interval of the trigger VPBs varied from 270 to 380 ms (325 ± 45 ms) and the interval from the earliest Purkinje potential to the onset of the VPB was from 126 to 160 ms (139 ± 18 ms). Bode et al.[10] and Enjoji et al.[36] have also reported the successful ablation of the Purkinje-related VF associated with acute coronary syndrome. Many investigators demonstrated the same approach with good results in remote MI or ischemic cardiomyopathy patients.[11–15] Szumowski et al.[11] and Marrouche et al.[12] emphasized the important role of the Purkinje fibers along the border zone of scar in the mechanism of polymorphic VT or VF post MI.

Electrophysiologic and Histopathologic Findings

Although the experimental studies have revealed that catheter ablation of the Purkinje system could terminate VF and prevent VF induction,[32,33,37,38] the role of the Purkinje system and anatomical relationship to the endocavitary structures, such as the papillary muscles or fibromuscular bands, have not been described in humans. We examined autopsy specimens from a patient with ischemic cardiomyopathy who underwent VT/VF ablation.[15]

Catheter ablation was performed for VT/VF storm in a patient with ischemic cardiomyopathy. Trigger VPB1 with an RBBB and superior axis morphology exclusively initiated VF and trigger VPB2 with an RBBB and inferior axis morphology initiated sustained monomorphic VT or nonsustained polymorphic VT. The sustained monomorphic VT (cycle length 335–340 ms) exhibited an RBBB and superior axis QRS configuration. During VPB1, a diastolic Purkinje potential was recorded from the left ventricular midseptum and preceded the onset of VPB1 by 20 ms and the proximal two electrodes of the ablation catheter recorded a Purkinje potential 10 ms earlier than the distal pair of electrodes (Figs. 10A and 11A). RF energy applications to that site eliminated VPB1 and the VF was totally suppressed. During sustained monomorphic VT, diastolic Purkinje potentials were recorded from the left ventricular inferior septum and preceded the onset of the QRS by 60 ms (Figs. 10B and 11B). An RF energy application to this site terminated the VT and the VT became noninducible. From the successful ablation site of VPB2, which initiated nonsustained polymorphic VT at the basal septum, a left bundle electrogram was recorded during sinus rhythm. During VPB2, the earliest Purkinje potential was recorded and preceded the onset of VPB2 by 70 ms (Figs. 12 and 11C). After the ablation, monomorphic VT, VF, and nonsustained polymorphic VT were totally abolished. Unfortunately, he died from pneumonia 1 month later. No VT or VF was observed until his death.

Gross examination of the heart revealed several areas of the left ventricular septum exhibiting dense fibrosis corresponding to the sites of the RF energy deliveries (Figs. 13A and B). At the successful ablation sites for the sustained monomorphic VT and VPB2, fibromuscular bands connecting the posterior papillary muscle and ventricular septum were recognized (Fig. 13C). Figure 14 shows the microscopic examination of the left ventricular septum and fibromuscular band, which was connected to the posterior papillary muscle. In the center of the fibromuscular band, rows of Purkinje cells were recognized. In this case, it would appear that the Purkinje system in the fibromuscular band and posterior papillary muscle may have played an important role in the initiation and perpetuation of the VF associated with ischemic cardiomyopathy.

Mechanism

It is presumed that during MI the Purkinje fibers are relatively resistant to ischemia as they are supplied by cavital blood, and the amount of glycogen in Purkinje fibers is much higher than that in myocardial cells.[39] The glycogen can be metabolized anaerobically, which may make Purkinje cells more resistance to hypoxia than working myocardial cells. These surviving Purkinje fibers crossing the border zone of the MI demonstrate heightened automaticity, triggered activity, and supernormal excitability, which, when coupled with prolongation of the action potential duration in this region, may result in the necessary milieu for polymorphic VT/VF.[28,39–41] The role of reentrant wavelets is discussed, as well as the concept of rotors with sustained electrical activity rotating around a functional barrier.[1–3] Microreentry in small parts of the Purkinje

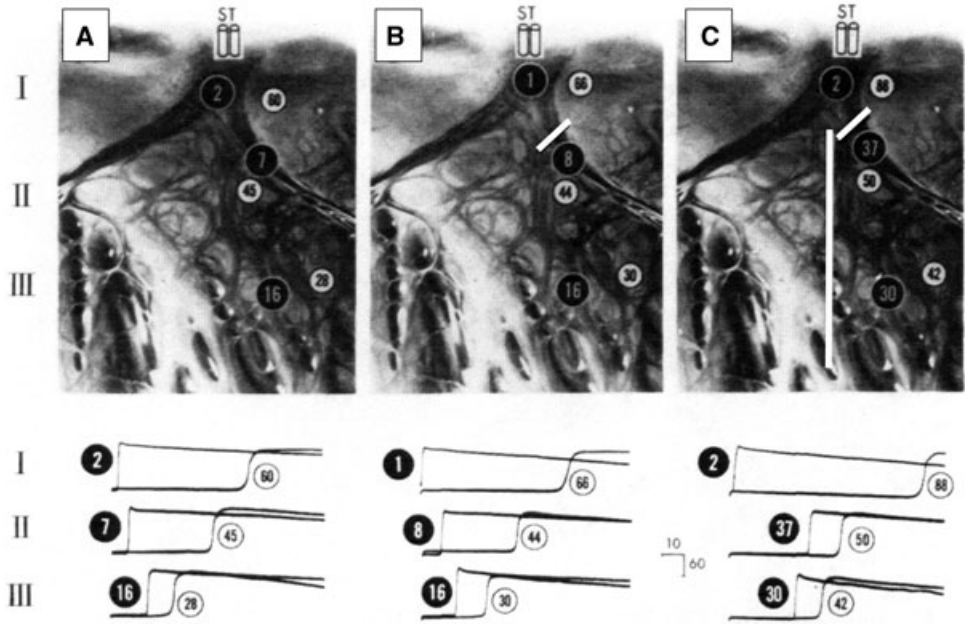

Figure 7. *Influence of the lesions in the left conducting system on the patterns of activation. (A) The preparation is of the left ventricle from the aortic ring to the beginning of the lower third of the septal surface. The anterolateral papillary muscle is on the left, and posteromedial papillary muscle is on the right. The pairs of action potentials at levels I, II, III were recorded from the corresponding levels on the photographs. The first of each pair is recorded from conducting cells and the second from muscle cells. The numbers represent the intervals from the stimulus to the response at each site. (B) The activation is remapped after the incision across the posterior division of the left bundle branch. (C) Mapping after another incision made vertically through the interconnecting subendocardial Purkinje fibers (see the text for further details). From Myerburg et al.[27] with permission.*

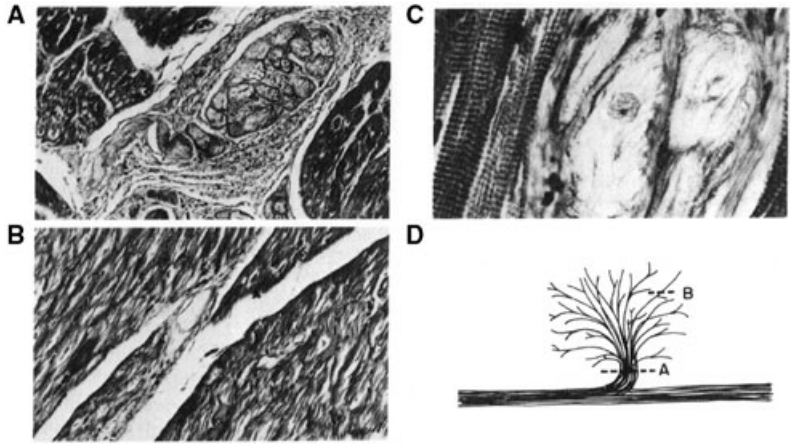

Figure 8. *Purkinje fiber distribution of the left ventricular free wall in the swine heart. (A) Subendocardial bundle of Purkinje fibers surrounded by a thick connective tissue sheath. (B) Two Purkinje fibers located in the subendocardium. (C) Purkinje fibers and neighboring cardiac muscle. The cytoplasm is generally clear, containing only a prominent nucleus and scattered fibrillar material. (D) Model of the Purkinje fiber distribution in the left ventricular free wall. The concentration of the fibers is greatest in the subendocardial layers, gradually thinning and branching out as the epicardial surface is approached. From Holland et al.[34] with permission.*

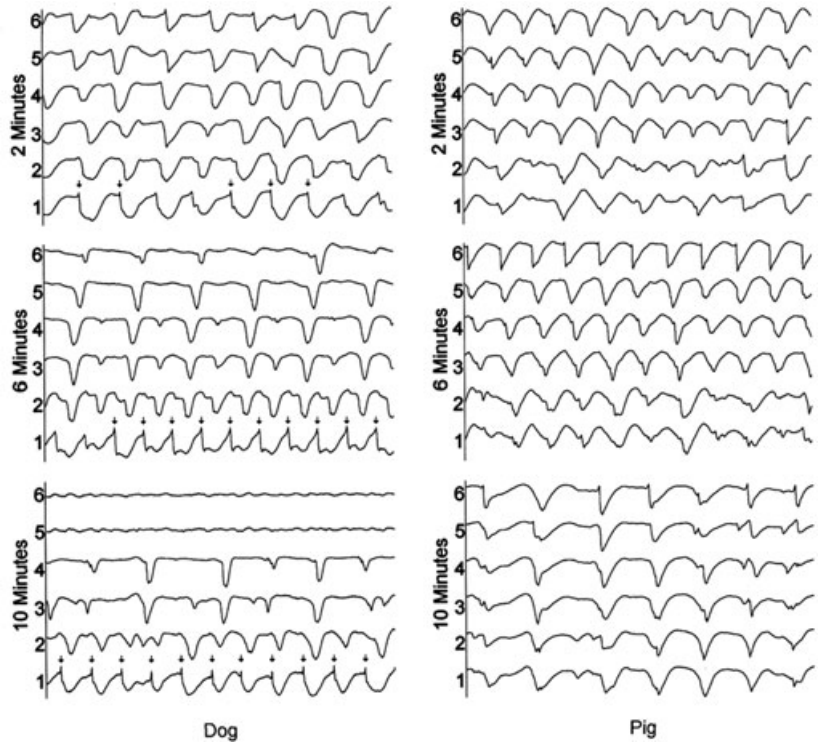

Figure 9. *Transmural activation at different durations of long-duration ventricular fibrillation (VF) in a dog and a pig. One second of data is shown. Electrode 1 is the most endocardial, while electrode 6 is the most epicardial. Conduction block occurs progressively closer to the endocardium in the dog as the VF continues with a continued fast-activating endocardium. Purkinje activations (arrows) precede working myocardial activations at the most endocardial electrode. Rapid activation remains present transmurally as the VF continues in the pig. From Allison et al.[35] with permission.*

network as the underlying mechanism of the VPBs has been suggested by Janse and Kleber.[42] However, detailed mapping and entrainment studies were impossible in the fast polymorphic VT/VF.

In patients with VF storm after an MI, which was reported by Bänsch et al., the coupling interval of trigger VPBs varied from 270 to 380 ms (325 $\pm$ 45 ms) and the interval from the earliest Purkinje potential to the onset of the VPB was 139 $\pm$ 18 ms.[7] In contrast to these patients after an MI, the coupling interval of the trigger VPBs in the patients without structural heart disease was 280 $\pm$ 26 ms and the interval from the Purkinje potential to the onset of the VPB was 38 $\pm$ 28 ms.[5] This may be related to a conduction delay between the Purkinje fibers and the myocardial tissue in ischemic conditions[43,44] or the difference in the origin in the Purkinje system.

Purkinje-Related VF in Other Heart Diseases

As with idiopathic VF and ischemic VF, a similar mechanism of VF initiation and ablative therapy has been demonstrated in other heart diseases. Sinha et al. demonstrated the mapping and ablation of VF in five patients with nonischemic dilated cardiomyopathy.[16] Electroatomic mapping identified scar along the posterior mitral annulus in all. The earliest site of the VPB activation was localized within the scar border zone and RF ablation was performed at this region targeting the Purkinje potentials around the scar border during sinus rhythm in four of the patients (Fig. 15). Mlcochova et al. reported two patients with repetitive VF associated with cardiac amyloidosis.[9] In one of the two patients, the earliest activation was recorded at the area of the proximal posterior fascicle of the left bundle during the trigger VPB. Of interest, the left myocardial voltage map was relatively normal without any low-voltage areas.

Bode et al. reported two patients with chronic myocarditis and a patient after an aortic valve replacement.[10] During the trigger VPB, one patient with chronic myocarditis had the earliest activation at the free wall of the right ventricle,

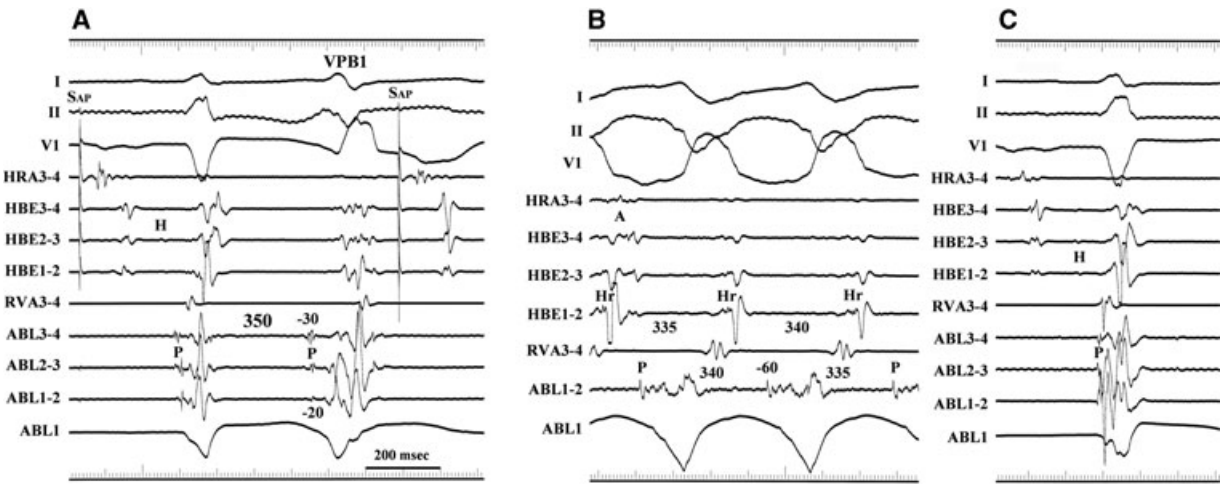

Figure 10. *Ablation of VF and sustained monomorphic VT in ischemic cardiomyopathy. (A) During VPB1, diastolic Purkinje potentials were recorded from the left ventricular midseptum and they preceded the onset of VPB1 by 20 ms. Purkinje potentials were also recorded during a basal atrial paced rhythm. Radiofrequency (RF) energy applications to that site eliminated VPB1. Note that the proximal two electrodes of the ablation catheter recorded the Purkinje potentials 10 ms earlier than the distal pair of electrodes during VPB1. (B) During sustained monomorphic VT, diastolic Purkinje potentials were recorded at the inferior septum and preceded the onset of the QRS by 60 ms. An RF application to that site terminated the VT. (C) During sinus rhythm, a fused Purkinje potential was recorded before the onset of the QRS. ABL = ablation catheter; H = His-bundle potential; HBE = His-bundle electrogram; Hr = retrograde conduction of the His-bundle during ventricular tachycardia; HRA = high right atrium; P = Purkinje potential; RVA = right ventricular apex; S_{AP} = atrial pacing stimulus. From Nogami et al.[15] with permission.*

and the other one at the basal midseptum of the left ventricle. The patient after an aortic valve replacement underwent a successful ablation of incessant VF at the left mid-inferior septum.

In 2003, Haïssaguerre et al. described the role in the induction of VF in a small number of patients with Brugada syndrome or long-QT syndrome who had frequent VPBs.[8] In my

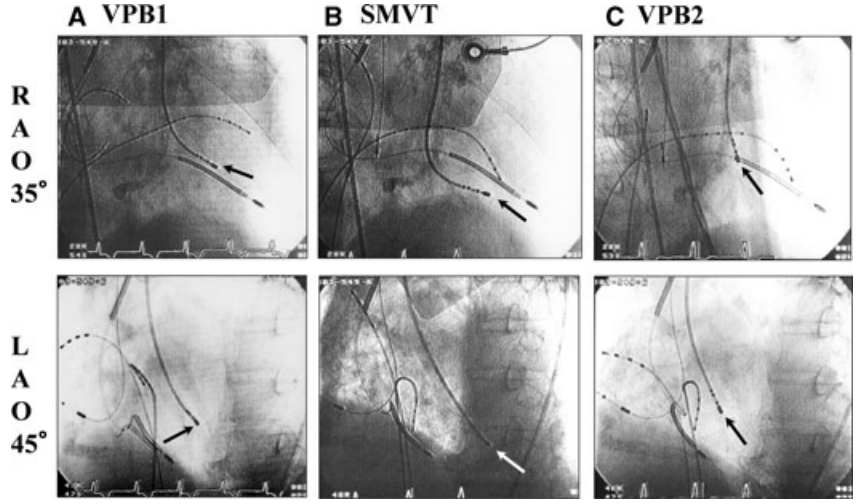

Figure 11. *Representation of successful ablation sites. (A) Successful ablation site of VPB1 with a right bundle branch block and superior axis morphology. (B) Successful ablation site of sustained monomorphic VT. (C) Successful ablation site of VPB2 with a right bundle branch block and inferior axis morphology. LAO = left anterior oblique view; RAO = right anterior oblique view; SMVT = sustained monomorphic ventricular tachycardia.*

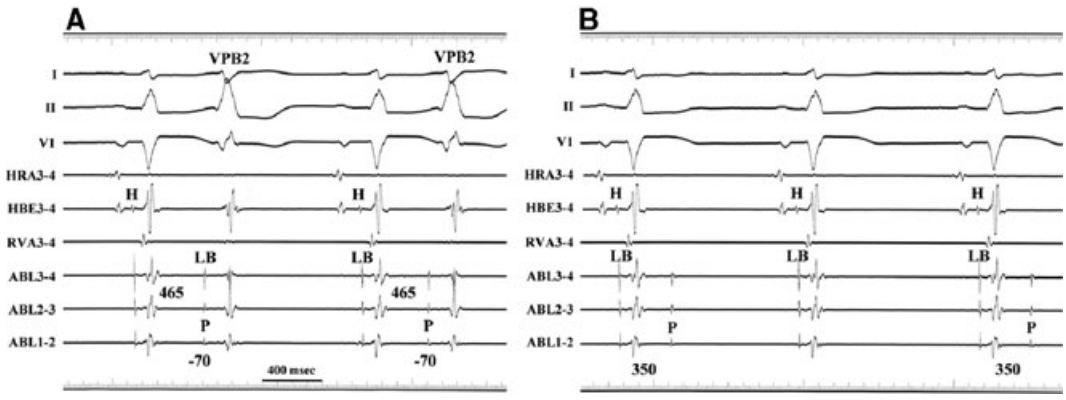

Figure 12. *Ablation of nonsustained polymorphic VT in ischemic cardiomyopathy. (A) From the successful ablation site of trigger VPB2 at the basal septum, a left bundle electrogram was recorded during sinus rhythm. During VPB2, the earliest Purkinje potential was recorded and it preceded the onset of VPB2 by 70 ms. (B) When the coupling interval of the Purkinje potential shortened to 350 ms, the conduction to the myocardium blocked. Note that this coupling interval is similar to that of VPB1 (Fig. 10A). LB = left bundle electrogram. From Nogami et al.[15] with permission.*

experience, Purkinje-like potentials were recorded from the right ventricular free wall during trigger VPBs in Brugada syndrome. However, the VPBs could not be eliminated by RF energy applications from the endocardium and the VF recurred shortly after the ablation. Whether the Purkinje system is related to the mechanism of polymorphic VT or VF in these syndromes or the trigger VPB is just Purkinje origin is still unknown.

CPVT is a lethal familial disease characterized by episodic syncope or sudden cardiac death occurring during exercise or acute emotional stress in individuals without structural cardiac abnormalities.[45] The underlying cause of these

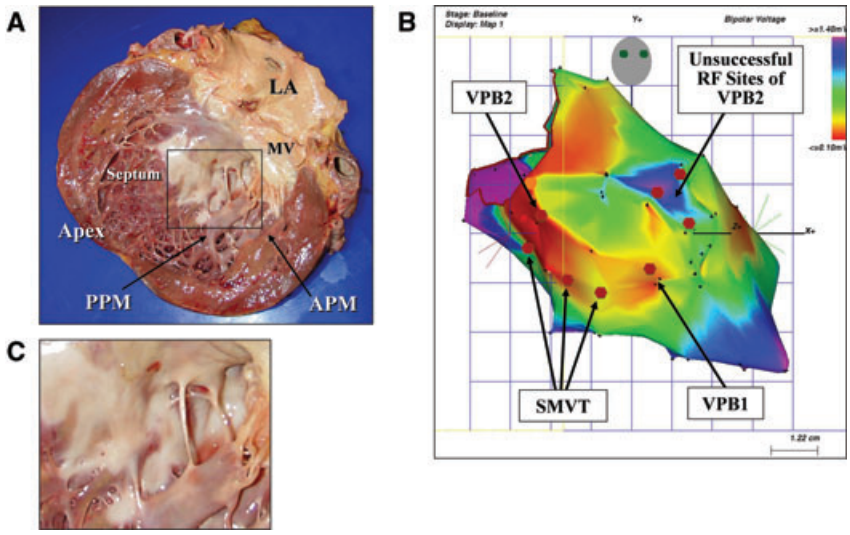

Figure 13. *(A) Gross examination of the heart revealed several areas of the left ventricular septum exhibiting dense fibrosis corresponding to the sites of the RF energy deliveries. (B) An electroanatomic voltage map revealed a low voltage area on the left ventricular septum. The red tags indicate all the ablation sites. (C) At the successful ablation sites of the sustained monomorphic VT and VPB2, fibromuscular bands connecting the posterior papillary muscle and ventricular septum were recognized. APM = anterior papillary muscle; LA = left atrium; MV = mitral valve; PPM = posterior papillary muscle; SMVT = sustained monomorphic ventricular tachycardia; VPB = ventricular premature beat. From Nogami et al.[15] with permission.*

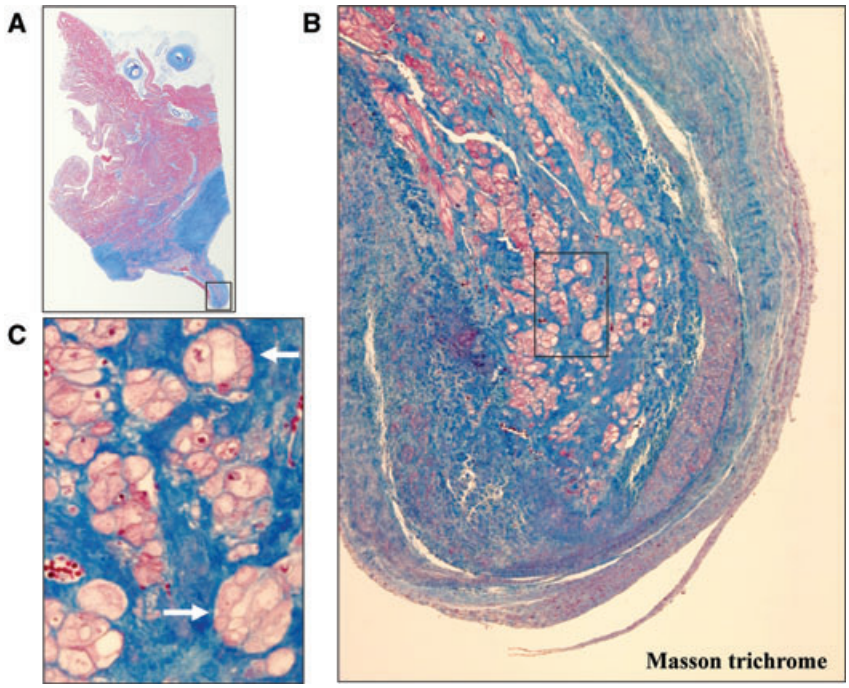

Figure 14. *Microscopic examination of the fibromuscular band connecting the posterior papillary muscle and ventricular septum. (A) The proximal portion of the fibromuscular band was examined. (B) and (C) In the center of the fibromuscular band, Purkinje cells were recognized. From Nogami et al.[15] with permission.*

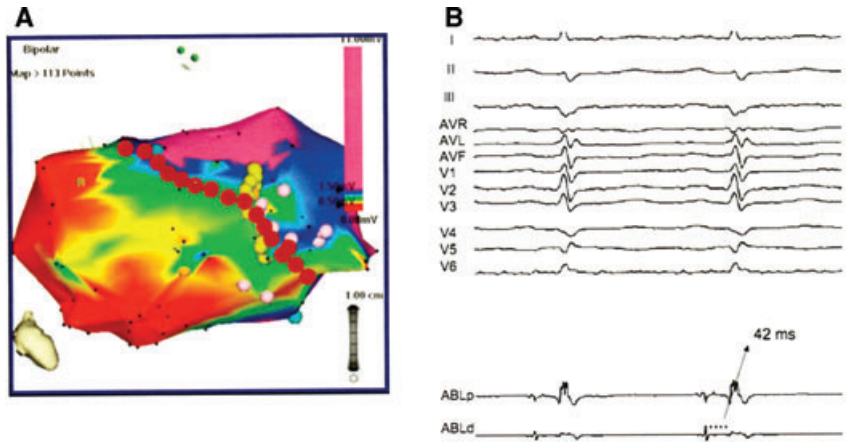

Figure 15. *Ablation of Purkinje VF in a patient with nonischemic dilated cardiomyopathy. (A) Electroanatomic map of the left ventricle. Scar (red) is identified as an area with a voltage < 0.5 mV, and normal tissue (purple) as a voltage >1.5 mV. Scar along the mitral annulus is seen. The red tags represent RF lesions, and pink tags fragmented signals. (B) Surface ECG and intracardiac electrogram during sinus rhythm recorded from the green point during mapping in panel A. There is a Purkinje-like potential inscribed 42 ms before the QRS. Purkinje-like potentials along the scar border were targeted for ablation. ABLp = ablation catheter proximal; ABLd = ablation catheter distal. From Sinha et al.[16] with permission.*

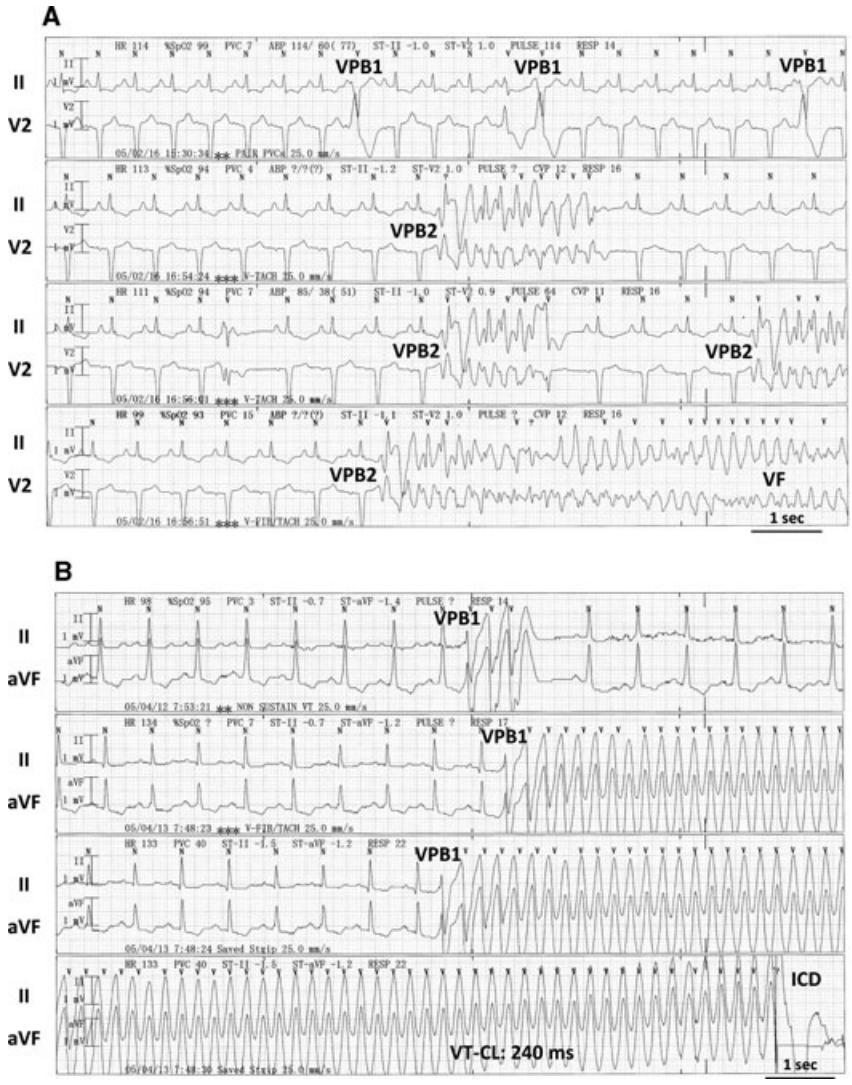

Figure 16. *Conversion from VF to rapid sustained monomorphic VT after VF ablation in a patient post myocardial infarction. (A) There were two VPBs. Both VPBs had a right bundle branch block configuration with a superior axis. While VPB1 was always isolated, VPB2 exclusively induced VF or nonsustained polymorphic VT. The ventricular tachyarrhythmia was always polymorphic VT or VF, and monomorphic VT was not observed. (B) Trigger VPB2 was successfully eliminated by the ablation of the scar border zone with preceding Purkinje potentials. Two months after the VF ablation, an ICD shock intervention occurred for "VF." ECG monitoring revealed that a rapid monomorphic VT (cycle length 240 ms) was initiated by VPB1 and terminated by an ICD shock. The QRS configurations of the monomorphic VT and VPB1 were similar. This rapid monomorphic VT was successfully ablated at the site with diastolic Purkinje potentials during VT. After the ablation, the VT became noninducible and VPB1 was also abolished.*

episodes is bidirectional VT, polymorphic VT, or VF. It is known to be associated with genetic mutations of the RyR2 or CASQ2 gene and CPVT is caused by an increased Ca^{2+} release through defective ryanodine receptor (RyR2) channels. Cerrone et al. demonstrated that the mechanism of CPVT was due to a focal origin in the Purkinje network in a knockin (RyR2) mouse model.[46] They found that the single Purkinje cells generated delayed afterdepolarization-induced triggered activity at lower frequencies and levels of adrenergic stimulation than the wild-type. Herron et al. also demonstrated that focally activated arrhythmias originated in the specialized electrical conducting

cells of the Purkinje system in a mouse model of CPVT.[47] Recently, Kaneshiro et al. first reported a successful ablation of CPVT.[17] They found bifocal origins in the left ventricle and one of the origins was preceded by Purkinje-like potentials.

Relationship between Polymorphic and Monomorphic VTs

In the Purkinje-related arrhythmias, there are polymorphic VT/VF and monomorphic VT. However, the difference in the clinical and electrophysiological characteristics between polymorphic VT/VF and monomorphic VT has not been determined. In some ischemic patients with primary VF (i.e., VF not preceded by monomorphic VT), sustained monomorphic VT also occurred before and/or after successful VF ablation.[7,10,15,36] Figure 14 shows the VF storm in a patient post MI. There were two VPBs. Both VPBs had an RBBB configuration with a superior axis. While VPB1 was always isolated, VPB2 exclusively induced VF or nonsustained polymorphic VT (Fig. 16A). The ventricular tachyarrhythmia was always polymorphic VT/VF, and monomorphic VT was not observed. The trigger VPB2 was successfully eliminated by ablation at the scar border zone with preceding Purkinje potentials. Two months after the VF ablation, an implantable cardioverter defibrillator (ICD) shock intervention for "VF" occurred. ECG monitoring revealed that a rapid monomorphic VT (cycle length 240 ms) was initiated by VPB1 and terminated by the ICD shock (Fig. 16B). The QRS configurations of the monomorphic VT and VPB1 were similar. This rapid monomorphic VT was successfully ablated at the site with a diastolic Purkinje potential during VT. After the ablation, the VT became noninducible and VPB1 was also abolished. It is interesting that these findings resemble the occurrence of a new atrial tachycardia after the ablation of persistent atrial fibrillation. Atrial tachycardia due to localized reentry may arise from a site in the vicinity of the prior ablation lesions for long-lasting persistent atrial fibrillation. Further, it is well known that atrial fibrillation sometimes converts into atrial flutter or atrial tachycardia after the administration of antiarrhythmic drugs. Tsuchiya et al. reported a case who exhibited a transition from a Purkinje-related polymorphic VT to a monomorphic VT after the administration of class Ic drugs.[48] The effect of catheter ablation or antiarrhythmic drugs might be associated with the "organization" of an unstable reentry circuit and the prolongation of the tachycardia cycle length.

Conclusions

Currently, there is no single hypothesis explaining the maintenance of VF. However, the Purkinje network may play an important role in the initiation and maintenance of VF or polymorphic VT in some patients with structurally normal hearts and several heart diseases. Because antiarrhythmic drug therapy leaves some patients unstable, or the time to stabilization may be prolonged, catheter ablation of the triggering VPBs from the Purkinje system should be used as an electrical bailout therapy in some patients.

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